REMARKS

Claims 1-11 are pending in the application. Claims 1-11 are rejected under 35 U.S.C. § 101 and under 35 U.S.C. § 112, first paragraph. Each of these rejections is addressed below.

Priority

The Examiner objected to the specification for failing to comply with conditions for receiving the benefit of an earlier filing date under 35 U.S.C. § 120, specifically, for failing to contain a reference to prior applications in the first sentence of the specification as required under 37 C.F.R. § 1.78(a)(2) and (a)(5). Applicants note that the priority information for this application is found at page 1 (lines 12-14), and this information, by the present amendment, now appears in the first sentence of the application.

Declaration

The Declaration was objected to as containing uninitialed and undated alterations. To address this objection, applicants submit herewith a new Declaration executed by Inventor Tan.

Drawings

The Office notes that the drawings as filed are unacceptable as having a background level that reduces clarity. To address this objection, Applicants submit herewith a set of formal drawings having a reduced background level.

Specification

The disclosure was objected to as containing embedded hyperlinks. Applicants have amended their specification to remove the noted hyperlink.

Rejection under 35 U.S.C. § 101

Claims 1-11, which are directed to methods for identifying a nematode having enhanced susceptibility to a pathogen, stand rejected on the ground that "the claimed invention is not supported by either a specific and substantial asserted utility or a well established utility." For the following reasons, applicants traverse this rejection.

The Utility Examination Guidelines (66 CFR 1092-1099) and Revised Interim Utility Guidelines Training Materials outline the criteria to determine the utility of an invention. The utility of an invention must be specific and substantial or well-established. In defining the metes and bounds of a specific utility, the Revised Interim Utility Guidelines Training Materials require that:

> a utility [be] specific to the subject matter claimed. This contrasts with a general utility that would be applicable to the broad class of the invention ... A general statement of diagnostic utility, such as diagnosing an unspecified disease, would ordinarily be insufficient absent a disclosure of what condition can be diagnosed (paragraph bridging pages 5 and 6; emphasis added).

By implication, therefore, the specific utility of a particular nematode identified using Applicants' claimed methods may be established by the disclosure of a specific disease or condition with which it is associated.

Likewise, a substantial utility is established by a "real world" context of use, such as the identification of a material that has a correlation to, or impacts the onset or progression of a particular disease or condition. Specifically, the Revised Interim Utility Guidelines state:

> both a therapeutic method of treating a known or newly discovered disease and an assay method for identifying compounds that themselves have a "substantial utility" define a "real world" context of use. An assay that measures the presence of a material which has a stated correlation to a predisposition to the onset of a particular disease condition would also define a "real world" context of use in identifying potential candidates for preventive measures or further monitoring (page 6; emphasis added).

Thus, a component of an assay method (such as a nematode identified using Applicants' claimed methods) for identifying candidate compounds which may be used for treating a specific disease itself has substantial utility. Similarly, components of an assay method for measuring the presence of a material associated with a risk of disease have substantial utility.

Alternatively, the utility requirement of 35 U.S.C. § 101 can also be satisfied by identifying a well established utility which is defined in the Revised Interim Utility Guidelines Training Materials as:

> A specific, substantial, and credible utility which is well known, immediately apparent, or implied by the specification's disclosure of the properties of a material, alone or taken with the knowledge of one skilled in the art (page 7; emphasis added).

Of course, in evaluating the utility of the invention, the credibility of the disclosure must be assessed. Credibility must be viewed from the perspective of a person of ordinary

skill in the art and should be based on the totality of the evidence (specification and prior art) and reasoning provided.

The Federal Circuit in *In re Brana*, 51 F.3d 1560 (Fed. Cir. 1995) has articulated the standard to be applied by the PTO in any challenge to an assertion of utility. In this case, the court stated:

> the PTO has the initial burden of challenging a presumptively correct assertion of utility in the disclosure. [citation omitted]. Only after the PTO provides evidence showing that one of ordinary skill in the art would reasonably doubt the asserted utility does the burden shift to the applicant to provide rebuttal evidence sufficient to convince such a person of the invention's asserted utility (page 1566; emphasis added).

The Office has failed to carry this burden. As discussed below, Applicants have asserted the specific and substantial utilities of identifying a nematode having enhanced susceptibility to a pathogen (i) to identify gene targets for the treatment of a pathogen-associated disease and (ii) to identify a compound that modulates host resistance as a treatment for a pathogen-associated disease. In addition, the utility of the nematodes identified using Applicants' methods is immediately apparent to one of skill in the art. Further, as is explained below, the Office has presented, in its rejection of the claims, no credible evidence that would cause a person of ordinary skill to doubt the asserted utilities of the present invention. On these bases, this rejection should be reversed.

First, Applicants, in their specification, disclose a well-established utility for the nematodes identified using the claimed methods. Applicants, for example, disclose that "the invention facilitates the identification of novel targets and therapeutic approaches for

preparing therapeutic agents active on host factors and genes that enable a host to mount its defense against pathogen invasion and infection (page 6, lines 33-36)." And, at page 22, lines 14-19, Applicants further disclose that the claimed methods provide "a simple means for identifying host factors and genes that enable a host to combat pathogen infection and compounds capable of either inhibiting pathogenicity or enhancing a host's resistance capabilities to such pathogens." Thus, Applicants' have asserted a specific, substantial, and credible utility with a real world context for the nematodes identified using Applicants' claimed methods.

In addition to identifying genes that promote pathogen resistance, the methods provide for the identification nematodes that can also be used in standard methods to identify compounds that stimulate or strengthen a host's resistance to a pathogen. As stated on page 6, lines 1-8, of the specification:

> The invention also provides long awaited advantages over a wide variety of standard screening methods used for distinguishing and evaluating the efficacy of a compound against virtually any number of pathogens. In one particular example, the screening methods described herein allow for the simultaneous evaluation of host toxicity as well as anti-pathogenic potency in a simple *in vivo* screen. Moreover, the methods of the invention allow one to evaluate .... the ability of the compound to stimulate and strengthen a host's response to pathogenic attack.

One skilled in the art would appreciate that compounds that strengthen a nematode's resistance to a pathogen are also useful for the treatment of diseases associated with pathogen infections. Again, the asserted utility of identifying compounds for the

treatment of a pathogen associated disease satisfies the criteria for a specific and substantial utility.

Finally, Applicants' well-established utility is immediately apparent to one skilled in the art, especially given the strong connection between the nematode experimental model system and the pathogenesis of disease found in man. Indeed, in recognizing the seminal work in *C. elegans* of the three winners of the 2002 Nobel Prize in Medicine and Physiology, the Nobel Assembly at the Karolinska Institutet stated:

> This year's Nobel Laureates in Physiology or Medicine [— Sydney Brenner, H. Robert Horvitz, and John Sulston—] have made seminal discoveries concerning the genetic regulation of organ development and programmed cell death. **By establishing and using the nematode *Caenorhabditis elegans* as an experimental model system, possibilities were opened to follow cell division and differentiation from the fertilized egg to the adult. The Laureates have identified key genes regulating organ development and programmed cell death and have shown that corresponding genes exist in higher species, including man. The discoveries are important for medical research and have shed new light on the pathogenesis of many diseases**. (Emphasis added.)

(http://www.nobel.se/medicine/laureates/2002/press.html; last visited December 15, 2003; a copy of the "Press Release: The 2002 Nobel Prize in Physiology or Medicine" is enclosed)

In addition to the work of Brenner, Horvitz, and Sulston, numerous scientific studies have utilized mutant nematodes as models for mammalian diseases and disorders. Exemplary studies are summarized in Appendix A, which highlights functionally and structurally conserved genes existing in nematode and mammalian pathways which serve to regulate aging, cell proliferation, cell death, insulin signaling, metabolism, and fat

storage. Indeed, nematodes having mutations in these pathways display a range of pathologies that parallel mammalian diseases, such as cancer, diabetes, obesity, and mucolipidosis.

Applicants also point out that, contrary to the Office's contention, one skilled in the art would in fact recognize that nematodes and mammals are susceptible to the same pathogens. For example, Ausubel (International Publication Number: WO 96/30053, copy enclosed) describes the infection of both nematodes and mice by the human pathogen *Pseudomonas aeruginosa* PA14. Applicants also point out that *Pseudomonas aeruginosa* PA14 is utilized in the experiments described throughout Applicants' specification. Accordingly, clear evidence exists that indicates that nematodes and mammals are susceptible to the same pathogens.

To substantiate its utility rejection, the Office, relies on Garrington et al., for the proposition that biochemical diversity exists among MAPK pathway members, and that diversity presumably renders difficult the correlation between nematode and mammalian disease or pathogens. Contrary to the Office's position, Applicants point out that Garrington accepts that nematodes having mutations in MAPK components are likely to have evolutionarily conserved mammalian counterparts. Garrington states:

> Genetic screens in *D. melanogaster* and *C. elegans* are defining the component members and complexity of organization of MAPK pathways. **Virtually every gene that is identified by mutagenesis screens in *D. melanogaster* or *C. elegans* has a mammalian counterpart** that has been cloned . . (Emphasis added.) (page 216, right column)

Given that Garrington accepts that MAPK pathway components identified in nematodes have mammalian counterparts whose structure and function is conserved, Garrington fails to support the Office's assertion that Applicants' claimed invention lacks utility.

The analysis to be carried out in making a rejection under 35 U.S.C. § 101 must include a determination of whether an assertion of utility has been made in an Applicants' specification and, if so, whether that asserted utility is credible (*i.e.*, whether the assertion of utility is believable to a person of ordinary skill in the art based on the totality of evidence and reasoning provided; M.P.E.P. § 2107.01-III(B)).

In the present case, Applicants have asserted the utilities described above. Applicants submit that, absent data to the contrary, it is credible that nematodes identified using Applicants' claimed methods are useful for identifying genes associated with disease resistance and for identifying compounds that stimulate or strengthen a host's resistance to a pathogen. Nonetheless, while the Office has stated that these utilities are not credible, no countervailing evidence, as is discussed above, has been presented that substantiates the Office's conclusion, as the Guidelines require. In particular, the Guidelines state that the Office

> must treat as true any statement of fact made by the Applicant in relation to the asserted utility, unless countervailing evidence can be provided that shows that one of ordinary skill in the art would have a legitimate basis to doubt the credibility of such a statement... [I]t is improper to disregard the opinion [of a qualified expert] solely because of a disagreement over the significance or meaning of the facts offered. (M.P.E.P. § 2107, emphasis added)

To be properly rejected under § 101, the Guidelines set forth that a case must represent one of those rare instances that meets the stringent criterion of being "totally incapable of achieving a useful result," *Brooktree Corp. v. Advanced Micro Devices, Inc.*, 977 F.2d 1555 (Fed. Cir. 1992), as cited in the Legal Analysis accompanying the Utility Examination Guidelines (M.P.E.P. § 2107.01-II). The only instances in which the federal courts have found a lack of patentable utility were where, "based upon the factual record of the case, it was clear that the invention could and did not work as the inventor claimed it did" (M.P.E.P. § 2107.01-II, emphasis added). These rare cases have been ones in which the applicant either (a) failed to disclose any utility for the invention, or (b) asserted a utility that could be true only "if it violated scientific principle, such as the second law of thermodynamics, or a law of nature, or was wholly inconsistent with contemporary knowledge in the art" (M.P.E.P. § 2107.02-IIIB).

Procedurally, the M.P.E.P. makes clear that the burden is on the Office to provide a detailed, reasoned explanation for the rejection that is supported, if possible, by documentary evidence indicating why the asserted utility is more likely than not "incredible." "An applicant's assertion of utility creates a presumption of utility" (M.P.E.P. § 2107.01-III(A)); "Where an applicant has specifically asserted that an invention has a particular utility, that assertion cannot simply be dismissed by Office personnel as being 'wrong,' even when there may be reason to believe that the assertion is not entirely accurate" (M.P.E.P. § 2107.01-III(B)). Conversely, if the Office determines that the claimed invention has a credible utility, neither a 35 U.S.C. § 101 nor

a related 35 U.S.C. § 112 rejection may be applied (or, upon rebuttal of the Office's position, both rejections must be simultaneously reversed).

In the present case, Applicants assert several utilities in the specification, that are, on their face, credible. Applicants also assert that the utility of the claimed invention is immediately apparent to one skilled in the art. Applicants' present invention provides for the identification of nematodes that can be used directly to identify potential therapeutics that promote host disease resistance. At least some of the identified compounds that promote such disease resistance are expected to have the proposed therapeutic activity of treating a pathogenic infection. No evidence has been made of record to dispute any of these utilities, and on this basis the rejection should be reversed.

Rejection under 35 U.S.C. § 112, first paragraph

Claims 1-11 also stand rejected under 35 U.S.C. § 112, first paragraph. In particular, the Office maintains that because the claimed invention is not supported by either a specific and substantial asserted utility or a well established utility one skilled in the art would not know how to use the claimed invention.

Given the uses of the claimed methods and nematodes described above, the related rejections under 35 U.S.C. § 101 and § 112, first paragraph should be withdrawn. As detailed above, Applicants have established a specific and substantial utility for methods of identifying nematodes having enhanced susceptibility to a pathogen, and have disclosed how such mutant nematodes are to be used in identifying components of a mammalian host-pathogen response pathway and in screening for therapeutic compounds

that enhance a mammalian response to a pathogen. It is noted that all such assertions must be shown to be incredible for this rejection to stand. It is Applicants' understanding that the Office will either provide a rebuttal for each of Applicants' assertions of utility or will withdraw these rejections in view of the above clarifications.

Claims 1-9 also stand rejected as lacking an adequate written description. In essence, the Office's rejection is based on the proposition that "the disclosed nematodes and MAPK components were not representative of the claimed genus." For the following reasons, this basis of the § 112 rejection is respectfully traversed.

The adequate written description requirement of 35 U.S.C. § 112, ¶ 1 provides that

> the specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same...

The written description requirement serves "to ensure that the inventor had possession, as of the filing date of the application relied on, of the specific subject matter later claimed by him; how the specification accomplishes this is not material." *In re Wertheim*, 541 F.2d 257, 262, 191 U.S.P.Q. 90, 96 (C.C.P.A. 1976). In order to meet the written description requirement, the applicant need not utilize any particular form of disclosure to describe the subject matter claimed, but "the description must clearly allow persons of ordinary skill in the art to recognize that [he or she] invented what is claimed." *In re Gosteli*, 872 F.2d 1008, 1012, 10 U.S.P.Q.2d 1614, 1618 (Fed. Cir. 1989) (citation omitted). Stated another way, "the applicant must . . . convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession of the

invention." *Vas-Cath, Inc. v. Mahurkar*, 935 F.2d 1555, 1563-64, 19 U.S.P.Q.2d 1111, 1117 (Fed. Cir. 1991).

The claims in question are generally directed to methods that include

Independent claim 1 reads:

> Claim 1. A method for identifying a nematode having enhanced susceptibility to a pathogen, said method comprising the steps of:
>
> (a) exposing a mutagenized nematode to a pathogen; and
>
> (b) determining survival of said mutagenized nematode when exposed to said pathogen, decreased survival of said mutagenized nematode relative to a non-mutagenized nematode identifying said mutagenized nematode as one having enhanced susceptibility to the pathogen.

Applicants' specification clearly describes to the skilled worker what is claimed. Claim 1 and dependent claims 2-9 are directed to *screening methods* for identifying nematodes having enhanced susceptibility to a pathogen. As described in Applicants' specification, the method involves exposing a mutagenized nematode to a pathogen and determining whether it has decreased survival relative to a non-mutagenized nematode. Contrary to the Examiner's assertions, Applicants' claims are not directed to a nematode having a mutation in a component of a MAPK pathway, although nematodes having such mutations would likely be identified by Applicants' claimed method.

Applicants clearly describe methods of screening for nematodes having enhanced susceptibility to a pathogen. For example, at pages 7-8, under the heading "Screen for *C. elegans* Mutants with Enhanced Susceptibility to PA14," Applicants describe methods for conducting an F2 screen to identify loss-of-function mutations in genes required for

the *C. elegans* pathogen defense response. Worms having enhanced susceptibility were identified by mutagenizing nematodes, exposing them to the pathogenic bacteria, PA14, and determining survival of the mutagenized nematodes relative to wild-type worms. Worms having decreased survival relative to wild type were identified as having enhanced susceptibility to a pathogen. Of the identified mutants, Applicants characterized (page 12, lines 9-26), mapped and cloned two exemplary mutants, *esp-2* and *esp-8*, which were identified as an MKK3/MKK6-type map kinase kinase (MAPKK) and a map kinase kinase kinase (MAPKKK), respectively (page 12, line 28, to page 13, line 31).

In sum, there can be no question that Applicants were in possession of the claimed genus at the time their application was filed, and that one skilled in the art would recognize Applicants' disclosure as a description of the invention defined by the present claims. As a result, Applicants' specification clearly satisfies the written description requirement, as set forth by the case law, and Applicants request reconsideration and withdrawal of this basis for the § 112 rejection.

CONCLUSION

Applicants submit that the claims are in condition for allowance, and such action is requested.

Enclosed is a Petition to extend the period for replying to the Office action for three months, to and including February 20, 2004.

If there are any charges, or any credits, please apply them to Deposit Account No. 03-2095.

Respectfully submitted,

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Appendix A

Conserved Pathway	Mammalian Disease/Condition	Nematode Defect	Reference
Insulin Signaling	Diabetes	Metabolic, longevity and developmental defects	Ogg et al., Nature 389:994-999, 1997
RAS Signaling and Rb Tumor Suppressor Pathways	Cancer	Vulval Induction Defects	Lu et al., Cell 95:981-991, 1998
Programmed Cell Death	Apoptotic Disorders (Retinal Degeneration, Cancer)	Cell Death Defects	Conradt et al., Cell 93:519-529, 1998; Xue et al., Nature 390:305-308, 1997
Lysosomal Pathway	Mucolipidosis	Lysosomal Defects	Hersh et al., PNAS 99:4355-4360, 2002
Fat Storage	Obesity	Fat accumulation Defects	Ashrafi et al., Nature 421:268-72, 2003
Rho GTPase Signaling Pathway	Faciogenital Dysplasia	Excretory Cell Defects	Gao et al., Human Molec. Genet. 10:3049-3062, 2001
Mesodermal Determination	Saethre-Chotzen Syndrome	Mesodermal defects	Corsi et al., Development 129:2761-2772, 2002